Claims

1. A modified cytokine ligand polypeptide comprising a modified amino acid sequence which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native amino terminal and carboxyl terminal amino acid residues of the native polypeptide are linked, directly or indirectly, together, characterised in that said ligand is provided with alternative amino terminal and carboxyl terminal amino acid residues and further wherein at least one binding domain for said ligand's cognate binding partner is disrupted.

2. A ligand according to Claim 1 wherein said ligand is selected from the group consisting of: growth hormone; leptin; erythropoietin; prolactin; tumour necrosis factor (TNF), interleukins (IL), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11; the p35 subunit of IL-12, IL-13, IL-15; granulocyte colony stimulating factor (G-CSF); granulocyte macrophage colony stimulating factor (GM-CSF); ciliary neurotrophic factor (CNTF); cardiotrophin-1 (CT-1); leukemia inhibitory factor (LIF); oncostatin M (OSM); interferon, IFNα and IFNγ, osteoprotogerin (OPG)

3. A ligand according to Claim 2 wherein said ligand is growth hormone.

4. A ligand according to any of Claims 1-3 wherein said native amino terminal and carboxyl terminal amino acid residues are directly linked to each other.

5. A ligand according to any of Claims 1-3 wherein said native amino terminal and carboxyl terminal amino acid residues are indirectly linked by a linking molecule.

6. A ligand according to Claim 5 wherein said linking molecule is a peptide linker.

7. A ligand according to Claim 6 wherein said linking peptide is a flexible peptide linker.

8. A ligand according to Claim 7 wherein said flexible linker is a polypeptide which comprises 5 to 30 amino acid residues.

9. A ligand according to Claim 8 wherein the linker comprises 10 to 20 amino acid residues.

10. A ligand according to any of Claims 6-9 wherein said linker comprises at least one copy of the peptide: Gly Gly Gly Gly Ser.

11. A ligand according to Claim 5 or 6 wherein said linker is an inflexible linker.

12. A ligand according to Claim 11 wherein said linker has, over at least over part of its length, a α-helical region.

13. A ligand according to any of Claims 1-12 wherein said receptor binding domain of said ligand comprises a low affinity bind site.

14. A ligand according to Claim 13 wherein said low affinity binding domain is site 2 of growth hormone.

15. A ligand according to Claim 14 wherein said low affinity binding domain of growth hormone is between about amino acid 116 – amino acid 122 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

16. A ligand according to Claim 15 wherein the alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 116 and amino acid 122 of human growth hormone as represented by Figure 1.

17. A ligand according to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 118 and amino acid 121 of human growth hormone as represented by Figure 1.

18. A ligand according to Claim 16 or 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 119 and amino acid 121 of human growth hormone as represented by Figure 1.

19. A ligand according to Claim 16 or 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 120 and amino acid 121 of human growth hormone as represented by Figure 1.

20. A ligand according to Claim 16 or 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 118 and amino acid 120 of human growth hormone as represented by Figure 1.

21. A ligand according to Claim 16 or 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 119 and amino acid 120 of human growth hormone as represented by Figure 1.

22. A ligand according to Claim 14 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between about amino acid 100 and amino acid 102 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

23. A ligand according to Claim 14 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between about amino acid 130 and amino acid 132 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

24. An oligomeric cytokine ligand polypeptide comprising at least two modified cytokine ligand polypeptides according to any of Claims 1-23 wherein said ligands are linked, either directly or indirectly, together.

25. An oligomeric ligand according to Claim 24 wherein said polypeptides are linked by a peptide linker comprising over at least over part of its length, a α-helical region.

26. An oligomeric ligand according to Claim 24 or 25 wherein said oligomer comprises two modified cytokine ligand polypeptides.

27. An oligomeric ligand according to Claim 26 wherein said oligomer comprises, at least 3; 4; 5; 6; 7; 8; 9; or at least 10 modified cytokine ligand polypeptides.

28. An oligomeric ligand according to Claim 26 wherein said oligomer comprises at least two modified growth hormone polypeptides.

29. An oligomeric ligand according to Claim 28 wherein said oligomeric growth hormone polypeptide comprises multiple ligand polypeptides.

30. An oligomeric ligand according to Claim 24 or 25 comprising at least one modified cytokine ligand polypeptide according to any of Claims 1-23 linked, either directly or indirectly, to at least one native cytokine ligand polypeptide from which said modified cytokine ligand polypeptide was derived.

31. An oligomeric ligand according to Claim 24 or 25 wherein said modified cytokine ligand polypeptide according to any of Claims 1-23 is linked to the extracellular ligand binding domain of said ligands cognate receptor.

32. An oligomeric ligand according to any of Claims 24-31 wherein said linker comprises a cleavage site.

33. An oligomeric ligand according to Claim 32 wherein said cleavage site is a proteolytic cleavage site.

34. An oligomeric ligand according to Claim 33 wherein said cleavage site is sensitive to a serum protease

35. An oligomeric ligand according to Claim 33 or 34 wherein said cleavage site comprises the amino acid sequence: LVPRGS, or functional variant thereof.

36. An oligomeric ligand according to Claim 33 or 34 wherein said cleavage site comprises at least one copy of the amino acid sequence: GGGGS, or functional variant thereof.

37. An oligomeric ligand according to Claim 36 wherein said cleavage site comprises the amino acid sequence PGI(S).

38. An oligomeric ligand according to Claim 33 or 34 wherein said cleavage site comprises the amino acid sequence: LVGPRGSPGI.

39. An oligomeric ligand according to Claim 36 wherein said cleavage site comprises at least two copies of the amino acid sequence GGGGS that flank said cleavage site.

40. An oligomeric ligand according to Claim 39 wherein said cleavage site is sensitive to the serum protease thrombin.

41. A nucleic acid molecule which encodes a modified cytokine ligand polypeptide according to any of Claims 1-23 or an oligomeric modified cytokine ligand polypeptide according to any of Claims 24-40.

42. A vector comprising a nucleic acid molecule according to Claim 41.

43. A cell transfected or transformed with a nucleic acid molecule or vector according to Claim 41 or 42.

44. A cell according to Claim 43 wherein said cell is a eukaryotic cell.

45. A cell according to Claim 44 wherein said cell is selected from the group consisting of: a mammalian cell; a yeast cell; an insect cell; or a plant cell.

46. A cell according to Claim 43 wherein said cell is a prokaryotic cell.

47. A non-human transgenic mammal transfected or transformed with the nucleic acid molecule or vector according to Claim 41 or 42.

48. A modified cytokine ligand polypeptide, an oligomeric modified cytokine ligand polypeptide, a nucleic acid molecule, a vector or a cell according any preceding Claim for use as a pharmaceutical.

49. A screening method to generate modified cytokine ligand polypeptides according to any of Claims 1-23 comprising the steps of:

i) forming a preparation comprising native cytokine ligand polypeptide molecules wherein the native amino terminal and carboxyl terminal amino acids are linked either directly or indirectly together;

ii) generating modified cytokine ligand polypeptide molecules wherein said molecules have alternative amino terminal and carboxyl terminal amino acids; and

iii) testing the activity of said modified cytokine ligand polypeptides.

50. A method according to Claim 49 wherein said native cytokine is growth hormone.

51. A modified cytokine ligand polypeptide identified by the method according to Claim 49.

52. A ligand according to Claim 51 wherein said modified cytokine ligand polypeptide is growth hormone.

53. A method of treatment of an animal, preferably a human, comprising administering an effective amount of a nucleic acid and/or vector and/or polypeptide and /or cell according to any previous Claim.